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Original Article

Cardiogoniometry can predict positive response to cardiac resynchronization therapy – A proof of concept study

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Background: According to American Heart Association guidelines, QRS duration and morphology are used to select patients for cardiac resynchronization therapy (CRT). But still there are some patients who are not responding to this device. We investigated whether the Cardiogoniometry (CGM) as a three-dimensional vectorcardiogram method can improve patient selection.
Methods: Echocardiography and CGM were performed for 25 consecutive patients with Left bundle branch morphology who were candidate for CRT implantation and were in sinus rhythm. Patients re-evaluated by echocardiography after 6 months post CRT implantation.
Results: The mean age of the patients was 63 ± 13 years and 17 (68%) were males. The mean LVEF was $19.4 \pm 7.4\%$ and $24.2 \pm 11.5\%$ before and after CRT implantation respectively. Median of the duration of the R loop before the R maximum demonstrated a negative correlation with the increase in LVEF, ($r = -0.36$, $P = 0.07$) and mean of maximal spatial velocity of the T-loop for all measured showed a positive correlation ($r = 0.39$, $p = 0.04$). Other parameters didn't show any significant differences.
Conclusions: Three-dimensional vectorcardiogram parameters can be helpful to predict the CRT response. Shorter duration of the R loop before the maximum R and smaller R loop area are predictors for responder patients.

1. Introduction

Delayed myocardial activation and contraction leading to cardiac dyssynchrony is one of the main mechanisms in chronic heart failure (HF). This dyssynchrony may further impair the ability of the heart to eject blood to the arterial system. In these patients, cardiac resynchronization therapy (CRT) is associated with improvement in cardiac function, reduction in the severity of ventricular dyssynchrony, an increase in left ventricular ejection fraction (LVEF), and a decrease in the left ventricular end systolic dimension.[1] This also results in an improved exercise capacity and reduction in rate of HF hospitalization and mortality.[2]

According to latest guidelines, QRS duration and morphology are used to select patients for CRT. CRT is recommended in patients with left bundle branch block (LBBB) despite optimal medical therapy as these patients have better outcomes.[3] Although majority of the treated patients show a benefit from CRT, approximately 30% of the patients do not show a significant reduction in left ventricular end systolic volume (LVESV) and clinical improvement.[4] Any tool to improve patient selection and prediction of responders to CRT may lead to maximize human and financial resource utilization and avoid the risk of associated complications.[5]

The electrocardiogram (ECG) morphology can be affected by geometrical factors such as heart position, orientation and geometry, body position, and respiration. It has been shown that heart rotation, strongly alters the ECG notching/slurring, intrinsicoid deflection time, and voltage-dependent parameter.[6] These limitations of standard 12-lead surface ECG can influence the interpretation of ECG findings, warranting emphasis on other techniques without this limitation. Cardiogoniometry (CGM), a

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noninvasive method for the quantitative three-dimensional analysis of myocardial depolarization and repolarization, augments the ability of the physician to analyze the recordings more accurately without the influence of heart rotation on most of its parameters.[7] Therefore, we investigated the role of CGM in predicting the CRT response.

2. Material and methods

2.1. Patient selection

Between March 2015 to April 2015, 29 consecutive patients with standard CRT criteria were enrolled in this study. The inclusion criteria were: (1) HF with New York Heart Association (NYHA) functional class II or III; (2) sinus rhythm; (3) QRS duration $\geq$120 ms with LBBB morphology; (4) LVEF $\leq$ 35%. LBBB was defined as QRS width $\geq$120 ms, a monophasic S wave in V1 (with or without a small r wave), and a monophasic R-wave in V6 with no Q wave.[8]

CRT device implantation was performed with a right ventricular (RV) lead in the RV apex or RV septum and left ventricular (LV) lead were implanted in one of lateral coronary veins with acceptable threshold, stable position, and no phrenic nerve stimulation.

This study was approved by our local ethical committee according to the Helsinki Declaration of the World Medical Association (2000). All patients were informed and gave written consent before the study.

2.2. Cardiogoniometry

All the patients underwent CGM (Cardiologic Explorer, **Enverdis** GmbH Medical Solutions, Germany; Model E12K34), at rest a few hours before CRT implantation. CGM recording was done for each patient in supine position and standard CGM leads were implanted.

CGM is a non-invasive technique for three-dimensional vectocardiography of the heart (http://www.enverdis.com/cardiogoniometry). The device analyses all the vectors and the waves of the heart signals and report more than 300 quantitative parameters automatically. The principles of the CGM have been published before.[9] By using four electrodes, the frontal and oblique sagittal plane (OSP) of the heart is defined. The X-axis, which has an anteroposterior (values with positive signs have a posterior location) orientation, and Y-axis, which has a left-oblique-sagittal basoapical (values with positive signs pointing to the apex) orientation, construct the OSP plane. The Z-axis is perpendicular to the X- and Y-axes. (Values with negative signs point up.) The Y- and Z-axes construct the frontal plane. The projection of the heart vector into each of these two orthogonal planes is done via three electrodes. Using the vector projections in the two orthogonal planes, the spatial display of electrical heart activity can be reconstructed for every millisecond (Fig. 1).

The analysis of all these data is fully automated by the CGM device and more than 300 parameters are calculated. These parameters can be divided into the following main classes: potential angles; time course; amplitude; shapes and eccentricities direction of vectors; potential distributions; and beat-to-beat variability for each P, R, and ST-T loop. Due to limitations of this study and small sample size we evaluated only 6 parameters of depolarization and repolarization in this study, listed in Table 1. We excluded all the P wave parameters and also beat-to-beat variations as they are not correlated with ventricular function and synchrony.

2.3. Echocardiography

Echocardiography (GE Vivid seven scanner equipped with an M3S multi-frequency phased array transducer) was performed immediately prior to device implantation as well as at follow up 6

Table 1
Demographic data of the patients.

Parameters	Mean ± SD or N (%)
Age (years)	63.2 ± 12.8
Sex (male)	17 (72%)
Non-ischemic Cardiomyopathy	14 (56%)
Baseline left ventricular ejection fraction	19.4 ± 7.4%
Baseline PR interval	147 ± 10
Baseline QRS width	158 ± 17

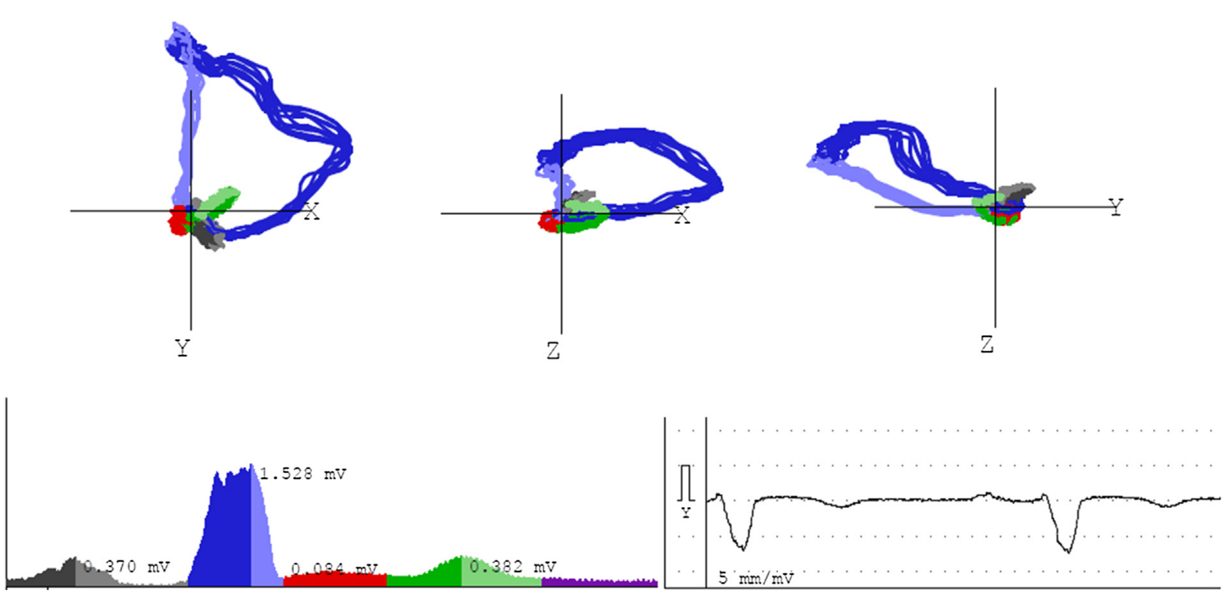

Fig. 1. Vectorgraphy recorded by the cardiogoniometry device in 3 orthogonal planes. The device analyses all these vectors and waves and reports more than 300 quantitative parameters automatically.
Cardiogoniometry (CGM), left ventricular ejection fraction (LVEF).

months later. LVEF was assessed by Simpsons' biplane method. Response to CRT was defined as ≥25% relative improvement in LVEF from baseline.[10,11]

2.4. Statistical analysis

Statistical analysis was performed with SPSS 15 for Windows (SPSS Inc., Chicago, Illinois). All variables were tested for normal distribution with Kolmogorov- Smirnov test. Continuous variables were presented as mean ± standard deviation (SD). Linear correlations between different predictors and change in LVEF were evaluated by Pearson's correlation coefficient. P values <0.05 were considered significant.

3. Results

There were 29 patients (15 ischemic cardiomyopathy and 14 non-ischemic cardiomyopathy) enrolled in this study at baseline, but three of them were lost to follow-up and the CGM of one of the patients was not appropriate for analysis due to patients' tremor. Thus, a total of 25 patients (17 male, mean age 63.2 ± 12.8) were studied (Table 1).

All the patients had typical LBBB in ECG; the mean QRS duration and the PR interval were 147 ± 10 and 158 ± 17 ms, respectively. The mean of LVEF before CRT implantation was 19.4 ± 7.4% and after 6-month's follow-up was 24.2 ± 11.5%. Eleven patients (44%) showed improvement in LVEF more than 25%. The correlation between CGM parameters and the changes in LVEF before and after 6 months of CRT was shown in Table 2. P11 showed the significant positive correlation with the increase of LVEF ($r = 0.39$, $P = 0.04$). The other CGM parameters did have no significant correlation with changes in EF ($P > 0.05$).

4. Discussion

With the overriding aim to establish a practical method to improve selection of patients for CRT implantation, this small pilot study tests some parameters derived from CGM and demonstrate that this 3D Vectorcardiography can predict hemodynamic response versus nonresponse to CRT in patients with LBBB. Although until now most studies have focused on the depolarization parameters for detection of responders, we found that there may be some repolarization parameters that can help us in detecting the responders.

4.1. Depolarization parameters

QRS duration as a reflection of total ventricular activation time and ventricular dyssynchrony is commonly used in daily practice for prediction of CRT responders. However, the QRS vector may provide additional information about this dyssynchrony. Each lead of the standard 12-lead ECG is only a projection of the heart vector along one axis. Therefore, the true vector amplitude may be missed. While in the vectorcardiogram, this vector can be followed continuously.

Previous data demonstrate that different vectocardiographic parameters may reflects electric interventricular dyssynchrony better than QRS duration. The maximum QRS vector amplitude, reflects electric interventricular dyssynchrony better than QRS duration irrespective of the presence of HF or myocardial infarction.[12] However, our data didn't show any benefit for maximum QRS vector amplitude or maximal spatial velocity of the R-loop.

The prognostic quality of the time interval between the maximum vector and the end of the vector loop showed to be relatively high with an excellent sensitivity for detection of responders in some studies.[13,14] This may be due to delayed depolarization of final parts of the left ventricle (mostly the posterolateral wall) that prolong the time between maximum vector and terminal deflections of QRS.[15] Although our study didn't show any relation between CRT response and the duration of the R loop after the R maximum, but it showed a negative correlation with the duration of the R loop before the R maximum. In other words, in a desynchronized left ventricle, if the first part of the left ventricle (mostly the septum) depolarizes normally, the patient may respond better after CRT implantation. As the LV pacing was performed from anterior, lateral, or posterior part of LV (according to the lead position) and not from the septum, this means that the fast septal depolarization by the intrinsic AV node conduction in conjunction with depolarization of the other parts by LV lead may improve the contraction further.

We also didn't find any relation between roundness of the R loop with and response to CRT.

4.2. Repolarization parameters

Although the QRS complex reflects the ventricular electrical activation and depolarization and consequent contraction, the repolarization phase of the myocardium may also provide additional information, since in this phase many ion channels, including those that regulate intracellular calcium concentrations, are involved. Also, there is some positive relation between T-wave area and QRS duration. It seems that T-wave area improvement predicts CRT response.[16,17] We found that maximum spatial velocity of the T-loop can also have a positive correlation with response to CRT. As shown by a computer modelling study, diffuse LV electrical uncoupling and LBBB both create a prolonged QRS duration on the ECG, but that the amplitudes of QRS complex and T-wave are considerably larger during LBBB compared to uncoupling.[18] Increased maximum T wave velocity may be a sign of highest T wave amplitude and be more compatible with LBBB.

Several categories of patients, such as females or patients with non-ischemic cardiomyopathy are known to respond better to CRT.[19–21] Regardless of the exact mechanism, differences in CGM and vectocardiography parameters in these patients may explain their better response to CRT.[9,22,23]

4.3. Study limitations

This is a first explorative study with relatively small sample size and must be followed by a prospective validation study. Also, only

Table 2
Correlation between CGM parameters and LVEF differences before and after of CRT.

CGM parameter	Definition	R	P
P168	Median of the duration of the R loop before the R maximum	−0.36	**0.07**
P169	Median of the duration of the R loop after the R maximum	0.15	**0.58**
P8	Mean of maximal spatial velocity of the R-loop for all measured	0.26	**0.2**
P11	Mean of maximal spatial velocity of the T-loop for all measured	0.39	**0.04**
P76	Median Rmax [mV]	0.27	**0.18**
P106	Median of the variable "eccentricity", which describes the roundness of the R loop	0.33	**0.1**

6 parameters of CGM were selected and evaluated while many other parameters were excluded. Further investigations with larger sample volumes and calculation of more parameters from CGM such as age difference of the patients and possible influence of the parameters of the ECG that are age dependent is needed, which can overcome the shortcomings of this study. We only defined LVEF as a parameter of response. This parameter has only a modest correlation with improvement with CRT.

5. Conclusions

Three-dimensional vectorcardiogram parameters can be helpful to predict the CRT response and consequently may improve patient selection for CRT device implantation.

Conflict of interest

The authors report no financial relationships or conflicts of interest.

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